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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,033	08/01/2001	Rosanne M. Crooke	ISPH-0592	5785

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EXAMINER	
EPPS -SMITH, JANET L	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/920,033	CROOKE, ROSANNE	
	Examiner	Art Unit	
	Janet L. Epps-Smith	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date. _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07-06-09 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 1, 8-10, 12-13, 20, 28-30, 33-35 and 40-43 were cancelled by Applicant. Newly added claims 44-63 are now pending for examination.

Response to Arguments

4. Applicant's arguments with respect to the rejections of claims 1, 8-10, 12-13, 20, 28, 29-30, 33-35, and 40-43 under 35 U.S.C. 103(a) are moot in response to Applicant's cancellation of these claims and the addition of new claims 44-63.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 44-52, 54-55, 58, 60, and 62 are rejected under 35 U.S.C. 102(e) as being anticipated by Hancock et al. (US 6534277).

7. Instant claim 44 recites the following:

44. (New) An oligonucleotide 12 to 30 nucleobases in length, or a salt thereof, targeted to a nucleic acid molecule encoding apolipoprotein B, wherein the oligonucleotide specifically hybridizes to a nucleic acid comprising SEQ 1D NO: 3 and wherein the oligonucleotide comprises at least 8 consecutive nucleobases of SEQ ID NO:27.

8. Hancock et al. discloses the following antisense oligonucleotide compound, see col. 45, lines 52-55: 5'-CAC CTG GTT G**TG TGC TAC CAT CC**T **A**CT-3' (SEQ ID NO:32). This antisense oligonucleotide is 12 to 30 nucleobases in length and comprises a 13 nucleobase consecutive stretch of SEQ ID NO: 27. Since the specification as filed does not define the phrase “specifically hybridizes” as having a specific degree of complementarity, absent evidence to the contrary, since the disclosed antisense oligonucleotide meets all of the other structural limitations of the claimed invention, the disclosed antisense would inherently possess all other functional characteristics.

9. The antisense oligonucleotides of Hancock et al. are described as follows:

"An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides or more in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (e.g., an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

10. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest).

11. Antisense nucleic acid molecules administered to a subject or generated in situ such that they hybridize with or bind to cellular mRNA encoding the polypeptide of interest to thereby inhibit expression, e.g., by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue, e.g., transplant or autoimmune lesion, site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically.....The antisense nucleic acid molecule can also comprise a 2'-O-methylribonucleotide or a chimeric RNA-DNA analogue (see cols. 46-47). "

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claim 44 and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by Sanchez-Pescador et al. (US 5618674).

14. This reference discloses SEQ ID NO: 62, having the following sequence: d(A-A-G-A-C-C-T-A-T-A-A-C-T-T-**C-T-A-C-C-A-T-C-C-C-A-T**-T-T-T-G). This sequence is 30 nucleobases in length and comprises a 12 nucleobase contiguous portion of SEQ ID NO: 27 of the instant application, and further comprises 14 identical nucleobases of SEQ ID NO: 27.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 44-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hancock et al. (US 6534277) in view of Monia et al. (US 5,656,612), Bennett et al. (US 6,172,216), and Wengel et al. (US 2002/0068708A1).

17. Hancock et al. (as applied to claims 44-52, 54-55, 58, 60, and 62, above) discloses the following antisense oligonucleotide, see col. 45, lines 52-55: 5'-CAC CTG GTT GTG TGC TAC CAT CCT ACT-3' (SEQ ID NO: 32). Hancock et al. does not teach wherein the disclosed oligonucleotide inhibits the expression of the long form of apolipoprotein B, ApoB-100, absent evidence to the contrary, since the disclosed antisense oligonucleotide meets all of the other structural limitations of the claimed invention, the disclosed antisense would inherently possess all other functional characteristics.

18. Hancock et al., however, does not teach wherein the 2' substituted sugar moiety is a bicyclic sugar moiety, or a locked nucleic acid, or wherein the nucleic acid comprises a 5' and 3' wing segment and further comprises a 2'-deoxynucleoside gap segment (see claim 56), or wherein the disclosed antisense oligonucleotide is in the form of a pharmaceutical composition further comprising a colloidal dispersion system.

19. Moreover, Monia et al. describe a variety of suitable carriers or formulations as pharmaceutically acceptable carriers, see e.g. col. 7, lines 41-59:

> Formulations for topical administration may include ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful.
>
> Compositions for oral administration include powders or granules, suspensions or solutions in water or non-aqueous media, capsules, sachets, or tablets. Thickeners, flavorings, diluents, emulsifiers, dispersing aids or binders may be desirable.
>
> Formulations for parenteral administration may include sterile aqueous solutions which may also contain buffers, diluents and other suitable additives.
>
> In addition to such pharmaceutical carriers, cationic lipids may be included in the formulation to facilitate oligonucleotide uptake. One such composition shown to facilitate uptake is Lipofectin (BRL, Bethesda Md.).

20. Bennett et al. teach that the incorporation of modified nucleobases into oligomeric compounds, including 5-methylcytosine modifications, is well known in the art for the purpose of increasing the binding affinity of the oligomeric compounds of the invention. (col. 9, lines 5-7). Bennett et al. also discloses wherein the oligonucleotide is a chimeric oligonucleotide, comprising 2'-MOE modifications (other positions comprise 2'-deoxy modifications), all 2'-MOE cytosines are 5-methylcytosines, and all linkages are phosphorothioate linkages. In Example 5 of Bennett et al. the following is disclosed:

Chimeric oligonucleotides, oligonucleosides or mixed oligonucleotides/oligonucleosides of the invention can be of several different types. These include a first type wherein the "gap" segment of linked nucleosides is positioned between 5' and 3' "wing" segments of linked nucleosides and a second "open end" type wherein the "gap" segment is located at either the 3' or the 5' terminus of the oligomeric compound. Oligonucleotides of the first type are also known in the art as "gapmers" or gapped oligonucleotides. Oligonucleotides of the second type are also known in the art as "hemimers" or "wingmers".

21. Bennett et al. also teaches that antisense compounds may encompass any pharmaceutically acceptable salt, which upon administration to an animal including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Moreover, the pharmaceutically acceptable salts of Bennett et al. encompass “salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto." Therefore, the disclosure of Bennett et al. encompasses oligomeric compounds comprising sodium salts; see for example, col. 11, lines 1-23. Additionally, Bennett et al. teach the pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present invention may also include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides.

22. Bennett et al. further teach that “colloidal dispersion systems” may be used as delivery vehicles to enhance the in vivo stability of the compounds and/or to target the compounds to a particular organ, tissue or cell type. Colloidal dispersion systems include, but are not limited to, macromolecule complexes, nanocapsules, microspheres, beads and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, liposomes and lipid:oligonucleotide complexes of uncharacterized structure. A

preferred colloidal dispersion system is a plurality of liposomes." The modified therapeutic oligonucleotides of Bennett et al. are disclosed as having increased nuclease stability and increased cellular uptake.

23. Wengel et al. provides a review of the benefits of designing oligonucleotide compounds to comprise Locked Nucleic Acid bicyclic sugar modifications. According to Wengel et al., oligonucleotides comprising this class of sugar modification are able to provide valuable improvements to oligonucleotides with respect to affinity and specificity towards complementary RNA and DNA oligomers (see abstract and page 3).

24. It would have been obvious to the ordinary skilled artisan at the time of the instant invention to modify the antisense compounds of Hancock et al. to comprise the modifications disclosed in Monia et al., Bennett et al. and Wengel et al.

25. One of ordinary skill in the art would have been motivated to make these modifications since Monia et al. teaches that these modifications are known to both increase hybridization efficiency and nuclease resistance of oligonucleotide compounds comprising these modifications. Moreover, Monia et al. teach that oligonucleotides comprising these modifications possess high target site specificity and increased cellular uptake in comparison to unmodified antisense oligonucleotides. Furthermore, one of ordinary skill in the art at the time of the instant invention would have been motivated to make this modification since the prior art teaches that antisense compounds comprising LNA modifications produces antisense compounds with stability towards exonucleolytic degradation, effective delivery into cells, and display

unprecedented binding affinity to both RNA and DNA (see Wengel et al., page 3, lines 25-35).

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Smith whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Smith/
Primary Examiner, Art Unit 1633